HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TheraCys safely and effectively. See full prescribing information for Theracys.

TheraCys®, BCG Live (Intravesical)
Initial U.S. Approval: 1990

WARNING - RISK OF TRANSMISSION AND INFECTION

See full prescribing information for complete boxed warning.

- **TheraCys®, BCG Live (Intravesical) contains live, attenuated mycobacteria. Because of the potential risk for transmission, prepare, handle, and dispose of TheraCys as a biohazard material. (2, 5)**
- **BCG is capable of dissemination when administered by the intravesical route. Serious infections, including fatal infections, have been reported in patients receiving Intravesical BCG. (5, 6)**

----------INDICATIONS AND USAGE----------

TheraCys is indicated for intravesical treatment and prophylaxis of urinary bladder carcinoma in situ (CIS) and for the prophylaxis of primary or recurrent stage Ta and/or T1 papillary tumors following transurethral resection (TUR). (1)

Limitation of Use: TheraCys is not recommended for

- Stage Ta low-grade papillary tumors, unless they are judged to be at high risk of recurrence. (1)
- Immunization against tuberculosis. (1)

----------DOSAGE AND ADMINISTRATION----------

For intravesical instillation only.

- Induction therapy: Administer one dose (81mg) TheraCys each week for 6 consecutive weeks. (2.1)
- Maintenance therapy: one dose given 3, 6, 12, 18 and 24 months following the initial dose. (2.1)

----------DOSAGE FORMS AND STRENGTHS---------

- One dose of TheraCys consists of one 81mg vial of freeze-dried Bacillus Calmette and Guérin (BCG) reconstituted and diluted in 50 mL sterile, preservative-free saline. (3)

----------CONTRAINDICATIONS----------

- Known systemic hypersensitivity reaction to any component of TheraCys or after a previous administration of TheraCys. (4.1)
- Immunosuppression due to congenital or acquired immune deficiencies, concurrent disease, cancer therapy, or immunosuppressive therapy. (4.2)
- Symptoms or a previous history of systemic BCG reaction. (4.3)
- Concurrent febrile illness, urinary tract infection, or macroscopic hematuria. (4.4)
- Active tuberculosis. (4.5)

----------WARNINGS AND PRECAUTIONS----------

- If TheraCys is administered within two weeks of either biopsy, TUR or traumatic bladder catheterization (associated with hematuria), a systemic BCG reaction is much more likely to occur. (5.1)
- If a bacterial urinary tract infection (UTI) occurs during the course of TheraCys treatment, withhold TheraCys instillation until complete resolution of the bacterial UTI. (5.3)
- If a patient develops persistent fever or experiences an acute febrile illness consistent with BCG infection, permanently discontinue BCG instillations. Initiate treatment with 2 or more antimycobacterial agents promptly while conducting diagnostic evaluation, including cultures. (5.2)
- Prepare and handle TheraCys using aseptic technique. Avoid needle stick injuries during the handling and mixing of TheraCys. (5.5)

----------ADVERSE REACTIONS----------

The most common adverse reactions observed with TheraCys treatment at a rate > 10% were transient dysuria, urinary frequency and urgency, malaise, hematuria, fever, chills, cystitis, and mild nausea.

Symptoms of bladder irritability were reported in approximately 50% of patients receiving TheraCys, typically beginning 4-6 hours after instillation and lasting 24-72 hours. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pharmacovigilance Department, Sanofi Pasteur Inc. at 1-800-822-2463 (1-800-VACCINE) or MEDWATCH at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Immunosuppressants interfere with the development of the immune response to TheraCys and increase the risk of disseminated BCG infection. (7.1)
- Antimicrobial therapy for other infections may interfere with the effectiveness of TheraCys. (7.2)
- Intravesical treatment with TheraCys may induce a positive response to a tuberculin skin test. (7.3)

----------USE IN SPECIFIC POPULATIONS ----------

Bladder capacity: There is an increased risk of bladder contracture when instilling TheraCys in patients with small bladder capacity. (8.6)

See 17 **for PATIENT COUNSELING INFORMATION**

Revised: [September 2013]

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF TRANSMISSION AND INFECTION

- **TheraCys®, BCG Live (Intravesical) contains live, attenuated mycobacteria. Because of the potential risk for transmission, prepare, handle, and dispose of TheraCys as a biohazard material. (2, 5)**
- **BCG is capable of dissemination when administered by the intravesical route. Serious infections, including fatal infections, have been reported in patients receiving Intravesical BCG. (5, 6)**

1 INDICATIONS AND USAGE

TheraCys is indicated for intravesical use in the treatment and prophylaxis of carcinoma *in situ* (CIS) of the urinary bladder and for the prophylaxis of primary or recurrent stage Ta and/or T1 papillary tumors following transurethral resection (TUR).

Limitation of Use: TheraCys is not recommended for

- Stage Ta low-grade papillary tumors, unless they are judged to be at high risk of recurrence.
- Immunization against tuberculosis.

2 DOSAGE AND ADMINISTRATION

For intravesical instillation only.

Do not inject intravenously, subcutaneously, intradermally or intramuscularly.

2.1 Dose and Schedule

Begin intravesical treatment of the urinary bladder a minimum of 14 days after biopsy or transurethral resection. Treatment consists of induction and maintenance therapy. For the induction therapy, administer one dose (81mg) of TheraCys each week for 6 consecutive weeks.

For the maintenance therapy, administer one dose at 3, 6, 12, 18, and 24 months following the initial dose.

2.2 Preparation

To avoid cross-contamination, do not prepare parenteral drugs in areas where TheraCys has been prepared. Handle and dispose of all equipment, supplies and receptacles in contact with TheraCys as biohazardous waste (or material). Wear gloves and eye protection and take precautions to avoid contact of BCG with broken skin. In addition, if the preparation cannot be performed in a biocontainment hood, wear a mask and gown.

Use aseptic techniques.

- Clean surface of the rubber stopper of the vial of TheraCys with a suitable antiseptic. Do not remove the rubber stopper from the vial.
- Using a syringe, draw up 3 mL of sterile preservative-free saline solution.
- Pierce the rubber stopper in the vial of freeze-dried material.
- Hold the vial of freeze-dried material upright and pull the plunger of the syringe back to create a mild vacuum in the vial.
- Release the plunger and allow the vacuum to pull the saline from the syringe into the vial of freeze-dried material. After all the saline has passed into the freeze-dried material, remove the syringe.
- Shake the vial gently until a fine, even suspension results. Avoid foaming since this will prevent withdrawal of the proper dose.
- Withdraw the entire contents (approximately 3 mL) of the reconstituted material into the syringe. Return the vial to an upright position before removing the syringe from the vial.
- Further dilute the reconstituted material from the vial (1 dose) in sterile**,** preservative-free saline to a final volume of 50 mL for intravesical instillation.
- Use TheraCys immediately after reconstitution. Any delay between reconstitution and administration must not exceed 2 hours at a temperature between 2° and 25°C (35° and 77°F).

Do not use any reconstituted product that exhibits flocculation or clumping that cannot be dispersed with gentle shaking.

Do not expose reconstituted product to sunlight, direct or indirect.

Keep exposure to artificial light to a minimum.

2.3 Administration

Insert a urethral catheter into the bladder under aseptic conditions, drain the bladder, instill 50 mL suspension of TheraCys slowly by gravity, and then withdraw the catheter.

Have the patient retain the suspension for as long as possible for up to two hours. During the first 15 minutes following instillation, the patient should lie prone. Thereafter, allow the patient to be in an upright position.

At the end of 2 hours, have the patient void in a seated position for safety reasons.

Instruct the patient to increase fluid intake in order to flush the bladder in the hours following BCG treatment.

2.4 Instructions for Disposal

Immediately place unused product, packaging, and all equipment and materials used for instillation of the product (e.g., syringes, catheters) in a container for biohazardous materials, and dispose of them according to local requirements applicable to biohazardous materials.

Properly dispose of voided urine during the 6 hr period following TheraCys instillation with an equal volume of 5% hypochlorite solution. [*See Patient Counseling Information (17)]*

3 DOSAGE FORMS AND STRENGTHS

One dose of TheraCys consists of one 81 mg vial of freeze-dried BCG reconstituted and diluted in 50 mL sterile, preservative-free saline.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Known systemic hypersensitivity reaction to any component [See *Latex (5.6)*and *Description* (*11*)] of TheraCys or after a previous administration of TheraCys or after a previous administration of TheraCys or a medicinal product containing the same substances is a contraindication to the administration of TheraCys.

4.2 Immunosuppressed Persons

Because of the risk of disseminated BCG infection, immunosuppressed persons with congenital or acquired immune deficiencies, whether due to concurrent disease (e.g., AIDS, leukemia, lymphoma), cancer therapy (e.g., cytotoxic drugs, radiation), or immunosuppressive therapy (e.g., corticosteroids) should not receive TheraCys. [See *Drug Interactions (7.1)*]

4.3 Systemic BCG Reaction

Do not use TheraCys in patients with current symptoms or a previous history of systemic BCG reaction. [See *Warnings and Precautions (5.1)*]

A minimum of 14 days must elapse before TheraCys is administered following biopsy, TUR, or traumatic catheterization.

4.4 Patients with Increased Risk of BCG Infection

Postpone TheraCys treatment until resolution of a concurrent febrile illness, urinary tract infection, or macroscopic hematuria.

4.5 Active Tuberculosis

Do not administer TheraCys to persons with active tuberculosis. Rule out active tuberculosis before starting treatment with TheraCys.

5 WARNINGS AND PRECAUTIONS

5.1 Systemic BCG Reaction

A systemic BCG reaction is a systemic granulomatous illness, which may occur subsequent to exposure to TheraCys. Because it is usually difficult to isolate BCG organisms from affected organs, the extent such a reaction is caused by an infectious process versus an inflammatory hypersensitivity reaction often is unclear. "Systemic BCG reaction" may be defined as the presence of any of the following signs, if no other etiologies for such signs are detectable: fever ≥39.5°C (≥103.1°F) for ≥12 hours; fever ≥38.5°C (≥101.3°F) for ≥48 hours; pneumonitis; hepatitis; other organ dysfunction outside of the genitourinary tract with granulomatous inflammation on biopsy; or the classical signs of sepsis, including circulatory collapse, acute respiratory distress, and disseminated intravascular coagulation. If TheraCys is administered within two weeks of either biopsy, TUR or traumatic bladder catheterization (associated with hematuria), a systemic BCG reaction is much more likely to occur. Death has been reported with the use of TheraCys in association with systemic BCG reaction in post-marketing experience.

5.2 BCG infection

To help prevent serious infections, avoid trauma and/or introduction of contaminants to the urinary tract. Wait a minimum of 14 days after traumatic catheterization before administering TheraCys. Resume TheraCys treatment according to the original schedule.

BCG infections of aneurysms and prosthetic devices (including arterial grafts, cardiac devices, and artificial joints) have been reported following intravesical administration of BCG. The risk of these ectopic BCG infections has not been determined. The benefits of TheraCys therapy must be carefully weighed against the possibility of an ectopic BCG infection in patients with pre-existing arterial aneurysms or prosthetic devices of any kind.

Some male genitourinary tract infections (orchitis/epididymitis) have been refractory to multiple drug antituberculous therapy and required orchiectomy.

Monitor patients for the presence of symptoms and signs of toxicity after each intravesical treatment. If a patient develops persistent fever or experiences an acute febrile illness consistent with BCG infection, permanently discontinue BCG instillations, evaluate and treat the patient

immediately for BCG infection, and seek an infectious diseases consultation. As standard therapy for BCG infection, promptly initiate treatment with 2 or more antimycobacterial agents while conducting diagnostic evaluation, including cultures. Do not use single antibiotic therapy. Negative cultures do not rule out infection.

TheraCys is not sensitive to pyrazinamide.

5.3 Bacterial Urinary Tract Infection (UTI)

If a bacterial urinary tract infection (UTI) occurs during the course of TheraCys treatment, withhold TheraCys instillation until complete resolution of the bacterial UTI.

5.4 Antimicrobial Therapy

Do not use antimycobacterial drugs (e.g., isoniazid) prophylactically to prevent the local, irritative side effects of TheraCys. They may affect the effectiveness of TheraCys and there are no data to suggest that the acute, local urinary tract symptoms common with intravesical BCG are due to mycobacterial infection.

5.5 Handling Precautions

Because TheraCys contains live mycobacteria, prepare, handle and dispose of TheraCys, and all equipment, supplies and receptacles in contact with TheraCys, as biohazardous waste (or material). Use aseptic techniques, wear gloves and eye protection, and take precautions to avoid contact of TheraCys with broken skin. Avoid needle stick injuries during the handling and mixing of TheraCys.
BCG infections have been reported in health care workers preparing BCG for administration. Nosocomial infections have been reported in immunosuppressed patients receiving parenteral drugs that were prepared in areas in which BCG was prepared.

5.6 Latex

The stopper of the vial for this product contains natural rubber latex, which may cause allergic reactions.

6 ADVERSE REACTIONS

The most common adverse reactions observed with TheraCys treatment at a rate > 10% were transient dysuria, urinary frequency and urgency, malaise, hematuria, fever, chills, cystitis, and mild nausea.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a medicinal product cannot be directly compared to rates in the clinical trials of another medicinal product and may not reflect the rates observed in practice.

Administration of TheraCys causes an inflammatory response in the bladder, thus requiring careful patient monitoring. Symptoms of bladder irritability are reported in approximately 50% of patients receiving TheraCys and typically begin 4-6 hours after instillation and last 24-72 hours. The irritative reactions usually are seen following the third instillation and tend to increase in severity after each administration. There is no evidence that dose reduction or antituberculous drug therapy can prevent or lessen the irritative symptoms of TheraCys.

In a clinical trial conducted in the United States, patients with stage Ta or T1 papillary tumor with 2 or more recurrences within the last 12 months, with carcinoma *in situ* (CIS), or with both of these conditions, were randomized to receive treatment with intravesical TheraCys or doxorubicin. Prior therapy with either BCG or doxorubicin was not allowed. Patients with muscle-invasive cancers or incomplete resection of papillary tumors were not eligible. One-hundred and twelve patients received TheraCys in 6 weekly instillations, followed by single instillations at 3, 6, 12, 18, and 24 months after enrollment, and were included in safety analyses. In the control group, 119 patients received doxorubicin in 5 weekly treatments, followed by 11 monthly treatments. Safety information was collected prior to each treatment dose.

Table 1 shows the frequency of adverse reactions observed in this trial. Local irritative symptoms were more common with TheraCys than with doxorubicin; however, grade ≥ 3 irritative toxicity was similar, occurring in approximately 2-7% of patients. Systemic symptoms (fever, chills, malaise, anorexia) were also more common with TheraCys. Overall, grade ≥ 3 toxicities were seen in 26 patients (23%) treated with TheraCys and 25 patients (21%) treated with doxorubicin. TheraCys treatment was discontinued in twelve patients due to toxicity.

Table 1: Adverse Reactions Reported in Patients Treated with TheraCys in a Trial Conducted in the United States

System/Organ Class Adverse reaction	Study Arm			
	TheraCys (N=112)		Doxorubicin (N=119)	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Infections and Infestations				
Cystitis	29.5	0	19.3	0.8
Urinary tract infection	17.9	0	17.6	0
Pulmonary infection	2.7	0	4.2	0.8
Systemic infection	2.7	1.8	0.8	0
Infection	0.9	0.9	0.8	0
Blood and Lymphatic System Disorders				
Anemia	20.5	0	24.4	0
Leukopenia	5.4	0	5.9	0
Coagulopathy/ Thrombocytopenia	0.9	0	0.8	0
Metabolism and Nutrition Disorders				
Anorexia	10.7	0	5.0	0
Nervous System Disorders				
Headache	1.8	0	3.4	0
Dizziness	0.9	0	0.8	0
Cardiac Disorders				
Cardiac (unclassified)	2.7	0	3.4	0.8
Gastrointestinal Disorders				

System/Organ Class Adverse reaction	Study Arm			
	TheraCys (N=112)		Doxorubicin (N=119)	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Nausea/Vomiting	16.1	0	8.4	0.8
Diarrhea	6.3	0	1.7	0
Abdominal pain	2.7	0	2.5	0
Constipation	0.9	0	0.8	0
Hepatobiliary Disorders				
Liver involvement	2.7	0	0.8	0
Skin and Subcutaneous Tissue Disorders				
Skin rash	1.8	0	2.5	0
Musculoskeletal, Connective Tissue, and Bone Disorders				
Arthralgia/Myalgia/ Arthritis	7.1	0.9	4.2	0
Flank pain	0.9	0	0.8	0
Renal and Urinary Disorders				
Dysuria	51.8	3.6	40.3	5.9
Urinary frequency	40.2	1.8	28.6	4.2
Hematuria	39.3	7.1	27.7	6.7
Urinary urgency	17.9	0.9	11.8	2.5
Renal toxicity (NOS)	9.8	1.8	9.2	0.8
Urinary incontinence	6.3	0	0.8	0.8
Bladder cramps/pain	6.3	0	5.0	1.7
Contracted bladder	5.4	0.9	5.0	0.8

System/Organ Class Adverse reaction	Study Arm			
	TheraCys (N=112)		Doxorubicin (N=119)	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Tissue in urine	0.9	0	1.7	0
Ureteral obstruction	0.9	0.9	0	0
Reproductive System and Breast Disorders				
Genital pain	9.8	0	13.4	1.7
General Disorders and Administration Site Conditions				
Malaise	40.2	1.8	14.3	0
Fever (>38°C)	38.4	2.7	9.2	0
Chills	33.9	2.7	5.9	0
Fatigue	0.9	0	0	0

6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post-approval use of TheraCys. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and Infestations

BCG Infection: BCG is capable of dissemination when administered by the intravesical route. Serious infections, including sepsis with associated mortality, have been reported. BCG infections have also been reported in eye, lung, liver, bone, bone marrow, kidney, regional lymph nodes, peritoneum, genitourinary tract (orchitis/epididymitis), and prostate (e.g., Granulomatous prostatitis). BCG infection of aneurysms and prosthetic devices (including arterial grafts, cardiac devices and artificial joints) has also been reported.

Joint symptoms (arthritis, arthralgia), ocular symptoms (including conjunctivitis, uveitis, iritis, keratitis, granulomatous choreoretinitis), urinary symptoms (including urethritis), skin rash, alone or in combination (Reiter’s syndrome), have been reported following administration of TheraCys. For the reports of Reiter's syndrome, the risk seems to be more elevated among patients who are positive for HLA-B27.

Renal abscess

Respiratory, Thoracic and Mediastinal Disorders

Pneumonia, interstitial lung disease

Skin and Subcutaneous Tissue Disorders

Erythema nodosum

Renal and Urinary Disorders

Renal failure, pyelonephritis, nephritis (including tubulointerstitial nephritis, interstitial nephritis and glomerulonephritis)

Urinary retention (including bladder tamponade and feeling of residual urine)

General Disorders and Administration Site Conditions

Flu-like symptoms

Investigations (Laboratory Tests)

Abnormal/increased blood creatinine or blood urea nitrogen (BUN)

7 DRUG INTERACTIONS

7.1 Immunosuppressive Treatments

Treatments using immunosuppressants, myelosuppressants, or radiation interfere with the development of the immune response to TheraCys and increase the risk of disseminated BCG infection.

Carefully consider TheraCys treatment decisions in patients with a condition that may require future mandatory immunosuppression (e.g., awaiting an organ transplant, myasthenia gravis).

7.2 Antimicrobial Therapy

Antimicrobial therapy for other infections may interfere with the effectiveness of TheraCys.

7.3 Clinical Test Interactions

Intravesical treatment with TheraCys may induce a positive response to a tuberculin skin test [tuberculin purified protein derivative (PPD)], which may complicate future interpretations of skin test reactions to PPD when used to diagnose suspected mycobacterial infections. If a patient's reactivity to PPD needs to be determined, the Tuberculin Skin Test should be conducted before administration of TheraCys.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with TheraCys. It is also not known whether TheraCys can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TheraCys should not be given to a pregnant woman unless clearly needed. Women should be advised not to become pregnant while on therapy.

8.3 Nursing Mothers

It is not known whether TheraCys can be excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from TheraCys in nursing infants, it is advisable to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of TheraCys for the treatment of superficial bladder cancer in pediatric patients have not been established.

8.5 Geriatric Use

In clinical studies with TheraCys, analyses evaluating the differences in safety and efficacy between study subjects 65 years of age and older versus younger subjects were not performed. No other data are available about the potential impact of age on the safety and efficacy of TheraCys.

8.6 Small Bladder Capacity

In patients with small bladder capacity, consider increased risk of bladder contracture when making the decision to treat with TheraCys.

10 OVERDOSAGE

Overdosage occurs if more than one vial of TheraCys is administered per instillation. If overdosage occurs, closely monitor the patient for signs of active local or systemic infection [See *Warnings and Precautions (*5*)*].

11 DESCRIPTION

TheraCys, BCG Live (Intravesical) is a freeze-dried preparation made from the Connaught strain of *Bacillus Calmette and Guérin*, which is an attenuated strain of *Mycobacterium bovis.*

The BCG organisms in the product are grown on media containing potatoes, glycerine, asparagine, citric acid, potassium phosphate, magnesium sulfate, ferric ammonium citrate, calcium chloride, copper sulfate, and zinc sulfate. Monosodium glutamate is added to the BCG organisms prior to freeze-drying.

Each vial of TheraCys contains 81 mg of freeze-dried BCG. The freeze-dried BCG does not contain any preservative.

One dose of TheraCys consists of one 81mg vial of freeze-dried BCG reconstituted and diluted in 50 mL sterile, preservative-free saline.

The BCG organisms from the vial are viable. *In vitro* potency is determined by an assay of live BCG organisms based on the number of colonies observed when grown on solid medium. The reconstituted product contains $10.5 \pm 8.7 \times 10^8$ colony-forming units (CFU) per vial.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

When administered intravesically as a cancer therapy, BCG promotes a local acute inflammatory and sub-acute granulomatous reaction with macrophage and lymphocyte infiltration in the

urothelium and lamina propria of the urinary bladder. The exact mechanism of action is unknown, but the anti-tumor effect appears to be T-lymphocyte-dependent.

14 CLINICAL STUDIES

The efficacy and safety of TheraCys were compared to doxorubicin hydrochloride in a multicenter, open-label, randomized clinical trial, in patients with carcinoma *in situ* (CIS) of the urinary bladder, recurrent Ta/T1 papillary tumors of any grade of the urinary bladder, or both. A total of 285 patients were randomized: 142 to treatment with doxorubicin (69 CIS and 73 non-CIS) and 143 to treatment with TheraCys (70 CIS and 73 non-CIS). All papillary tumors were completely resected prior to trial entry. TheraCys was administered intravesically weekly for 6 weeks, with additional single instillations at 3, 6, 12, 18, and 24 months following the initiation of treatment (total of 11 instillations over 2 years). The initial treatment with doxorubicin was given within 3 days of TUR, followed by 4 weekly treatments and then by 11 monthly treatments (total of 16 instillations over 1 year). Cytology and cystoscopy were obtained every 3 months for 2 years. Disease-free survival and 2-year disease-free survival were evaluated and an intent-to-treat analysis was performed.

The median age of patients treated with doxorubicin was 70 years (CIS; range 31-88 years) and 65 years (non-CIS; range 38-95 years), while the median age was 66 years (CIS; range 33-83 years) and 67 years (non-CIS; 24-95 years) in patients treated with Theracys. The racial distribution was 89% White, 5% Black and 6% Other in the doxorubicin treatment arm and 95% White, 3% Black and 2% Other in the Theracys treatment arm.

For patients with CIS, the complete response rate (i.e., negative biopsies and urine cytology) within 6 months of the initiation of treatment was 33% with doxorubicin and 71% with TheraCys ($p < 0.001$, Fisher's Exact Test). The probability of being disease-free at 2 years was 23% with doxorubicin and 51% with TheraCys ($p < 0.001$, Z Test). The median disease-free survival was 4.9 months for doxorubicin and 30 months for TheraCys ($p < 0.001$, Log Rank Test).

For patients with Ta/T1 papillary tumors only, the 2-year disease-free survival was 29% with doxorubicin and 50% with TheraCys (p = 0.008, Z Test). The median disease-free survival was 10.5 months with doxorubicin and 22.5 months with TheraCys (p = 0.001, Log Rank Test). The results are summarized in Table 2.

Table 2: TheraCys Efficacy in a Clinical Trial Conducted in the United States

	Carcinoma *in situ*		**Ta/T1 Papillary Tumors**	
	Doxorubicin N = 69	**TheraCys N = 70**	**Doxorubicin N = 73**	**TheraCys N = 73**
Complete Response	23 (33%)	50 (71%)	-	-
Median Disease-free Survival*	4.9 Months	30 Months	10.5 Months	22.5 Months
2-Year Disease-free Survival*	23%	51%	29%	50%
95% Confidence Interval	(15%, 35%)	(41%, 65%)	(20%, 41%)	(39%, 63%)

* Based on Kaplan-Meier estimates.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Vial, 1 dose of the freeze dried product. NDC No. 49281-880-58; in package of 1 vial, NDC No. 49281-880-03

16.2 Storage and Handling

- Store at 2 to 8 °C (35 to 46 °F).
- Do not expose to sunlight, direct or indirect.
- Keep exposure to artificial light to a minimum.
- Do not use beyond the expiration date.

17 PATIENT COUNSELING INFORMATION

- Inform patients to notify their physicians if they have any of the following symptoms that last more than 48 hours or increase in severity: fever, chills, malaise, flu-like symptoms, increased fatigue, or an increase burning or pain on urination.
- Inform patients to notify their physicians right away if they experience any of the following: increased urinary urgency or frequency of urination, blood in urine, joint pain, eye pain, irritation, or redness, cough, skin rash, jaundice, or vomiting.
- Inform patients that TheraCys contains live mycobacteria that can be present in voided urine. Advise patients on proper procedures to minimize environmental contamination of voided urine.
    - For 6 hours after treatment, void while seated to minimize splashing of urine.
    - For 6 hours after treatment, disinfect voided urine by adding an approximately equal volume of household bleach (5% hypochlorite solution) into the toilet bowl and allowing the bleach and urine to stand for 15 minutes prior to flushing.
    - Family and close contacts should avoid contact with voided urine.
- Increase fluid intake to flush the bladder for several hours after treatment with TheraCys, unless medically contraindicated.

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